Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 2, 27-41, 43-47, 49, 50, 52-55, 60, 61, 78-80, 82-93, and 96 are pending in the application, with 1, 46, 49, and 52 being the independent claims.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 112

Claims 1, 2, 27-41, 43-47, 49, and 50 have been rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for gossypol compounds that have aldehyde groups and isopropyl groups, allegedly does not reasonably provide enablement for apogossypol and Schiff's base derivatives of gossypol that do not have an aldehyde group on the gossypol compounds. (Office Action, p. 2). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that Shelley *et al.* (Anticancer Drugs, 11:209 (2000)) teach that apogossypol and Schiff's base derivatives of gossypol are inactive against tumor cell lines, due to the fact that the aldehyde groups are missing. (Office Action, p. 3). The Examiner also alleges that Shelly *et al.* teach that the ethyl derivatives of gossypol show negligible inhibitory activity. (Office Action, p. 3).

Applicants respectfully disagree. Shelley *et al.* do not teach that apogossypol is inactive as an anticancer agent. Rather, Shelley *et al.* show that apogossypol is capable of killing cancer cells, although with low potency (viability reduced by 15% in 24 hours) as measured in their assay (p. 212, col. 2). Further, Shelley *et al.* do not state that gossypol-related compounds require aldehyde groups for cytotoxicity, they only theorize that gossypol cytotoxicity may be induced by the reaction of the aldehyde groups with molecules essential for cellular function (p. 214, col. 2). Therefore, Shelley *et al.* do not provide evidence that the claimed invention is not enabled. They merely show that, in the assay they used for the time period they tested, the

concentration they used, and the cell lines they used, apogossypol had less anticancer activity than gossypol. This is insufficient evidence to prove that the claimed method of treating hyperproliferative disease with apogossypol lacked enablement and shows that the present application was in fact enabled at the time of filing.

Becattini *et al., Chem. Biol. 11*:389 (2004) teach that apogossypol is capable of binding and inhibiting Bcl-2 and Bcl-X_L with high affinity and induces apoptosis of tumor cell lines. Becattini *et al.* show higher levels of anticancer activity for apogossypol than Shelley *et al.*, most likely because they used a far more sensitive flow cytometry-based assay for detecting cell death. Thus, Becattini *et al.* merely confirms what was already shown by Shelley *et al.* and what was enabled by embodiments of the present specification, that apogossypol can be used for the treatment of hyperproliferative disease.

The Examiner alleges that Becattini *et al.* is not probative evidence for enablement because enablement has to be established at the time of filing. (Office Action, p. 3-4). While Applicants agree that a claimed invention must be enabled at the time of filing, Applicants assert that Becattini *et al.* is probative evidence of enablement even though it is a post filing date reference. The ability to induce apoptosis in cancer cells is an inherent characteristic of apogossypol, even if it was not generally recognized prior to the filing of the present application. Applicants' assertion in the present application that apogossypol can be used to treat hyperproliferative disease is based on this activity of the compound. Becattini *et al.* merely confirm that the present application was enabling at the time it was filed, as Becattini *et al.* demonstrate the anticancer activity of apogossypol under conditions that do not differ from the methods described in embodiments of the present specification. Thus, the present application is enabling for methods of using apogossypol to treat hyperproliferative disease.

The Examiner further alleges that Shelley *et al.* disclose that the ethyl derivatives of gossypol show negligible inhibitory activity to tumor cell lines similar to that of Schiff's base derivatives. (Office Action, page 3). This is an incorrect interpretation of Shelley *et al.* The passage at p. 214, col. 2, paragraph 2 refers to studies disclosed in reference 27 (Liang *et al.*, *Invest. New Drugs 13*:181 (1995)) on Schiff's bases of gossypol, including the ethylamine,

propylamine, isopropylamine and butylamine Schiff's base. A careful reading of Shelley *et al.* confirms this, as they state "[i]n this study[27] four bis Schiff's bases of racemic gossypol were synthesized and evaluated for anti-proliferate activity" (p. 214, col. 2, paragraph 2). Shelley *et al.* then go on to describe the results obtained in Liang *et al.*, that the isopropylamine Schiff's base of gossypol had anticancer activity comparable to gossypol and the other three Schiff's bases of gossypol had negligible activity. Thus, Shelly *et al.* and Liang *et al.* are referring to the ethylamine Schiff's base of gossypol and not the compound ethylgossypol of the present claims. The Examiner has no basis to state that the present claims as directed to the use of ethylgossypol for the treatment of cancer lack enablement.

It is respectfully requested that the rejection of claims 1, 2, 27-41, 43-47, 49, and 50 under 35 U.S.C. § 112, first paragraph be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 52-55, 60, 61, 78-80, 82-93, and 96 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Flack *et al.* (U.S. Patent No. 6,114,397) in view of Merck Manual of Diagnosis and Therapy. (Office Action, p. 5). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that one of ordinary skill in the art would have been motivated to employ both radiation and the gossypol compounds of Flack *et al.* in a method of treating cancer since both radiation and gossypol are known to be useful in treating cancer individually and combining them would be expected to produce at least an additive effect. (Office Action, p. 6).

Applicants respectfully disagree. Claim 52 is directed to methods of treating or ameliorating cancer comprising administering a gossypol compound selected from racemic or (-)-gossypol or racemic or (-)-gossypol acetic acid and one or more second agent(s) selected from docetaxel, paclitaxel, and/or radiation, wherein the combination of a gossypol compound and a second agent produces a synergistic effect with respect to one or more of tumor shrinkage, tumor

loss, time to tumor progression, or survival. Flack *et al.* do not disclose any examples of combination treatment with gossypol and docetaxel, paclitaxel, and/or radiation, and therefore do not show a synergistic response to combination treatment with respect to one or more of tumor shrinkage, tumor loss, time to tumor progression, or survival. As the Examiner stated, one of ordinary skill in the art reading Flack *et al.* might find it obvious to try a combination of gossypol with docetaxel, paclitaxel, and/or radiation for the treatment of cancer (although Applicants believe there is no motivation for such an attempt). However, one would not have a reasonable expectation that the particular claimed combinations of gossypol compounds with the specified anticancer agents or radiation produce a synergistic effect with respect to the specified outcomes. Thus, there is no *prima facie* case of obviousness of claim 52 and dependent claims 53-55, 60, 61, 78-80, 82-93, and 96 over the cited art.

In contrast, the present specification discloses the unexpected synergistic effects of combinations of gossypol compounds with docetaxel, paclitaxel, and radiation in treating or ameliorating cancer. See, *e.g.*, Examples 12, 16, 18, 19, 20, and 22 and Tables 8-11, 14, and 15. (-)-Gossypol shows clear synergistic effects with multiple anticancer agents. Racemic gossypol is less potent than (-)-gossypol but still provides a synergistic effect when combined with anticancer agents (see Fig. 19). Gossypol acetic acid is a composition containing gossypol with acetic acid as a solvate and is known in the art to exhibit the same activity as gossypol. The claims as amended are commensurate in scope with the unexpected synergistic results shown in the specification. Therefore, any alleged *prima facie* case of obviousness is overcome by this showing.

The Examiner alleges that the synergistic effect is not seen in all cases, citing the example in Fig. 16, where the breast cancer cell survival rate for (-)-gossypol is similar to that of taxol plus (-)-gossypol when the concentration of (-)-gossypol is above 10 μM. (Office Action, p. 8).

Applicants respectfully disagree. Applicants claim a method of treating or ameliorating cancer in a subject by administering a form of gossypol and a second agent wherein the combination produces a synergistic effect. Applicants are not required under the patent law to

demonstrate that a synergistic effect is produced at every single dosage amount of every single combination. Fig. 16 shows that, at concentrations below 10 μM gossypol, a clear synergistic effect of the combination of (-)-gossypol and taxol is produced in terms of killing cancer cells. Such a showing is sufficient to satisfy the present claims.

The Examiner further alleges that the scope of the claims is much broader than that of the showing because the examples are limited to (-)-gossypol, the cancer showing is limited, and the secondary agents are essentially limited to taxol. (Office Action, p. 8).

Applicants respectfully disagree. A synergistic effect for the combination of racemic gossypol and docetaxel (TAXOTERE) is shown in Example 16 and Figure 19. A synergistic effect for the combination of (-)-gossypol and docetaxel is shown in Examples 12, 16, and 22 and Figs. 16, 18, and 43B. A synergistic effect for (-)-gossypol in combination with paclitaxel (TAXOL) is shown in Example 12. A synergistic effect for (-)-gossypol in combination with radiation is shown in Examples 19 and 20, Figs. 36 and 38, and Table 18. The synergistic effects of various combinations on cancer cell killing is shown for breast cancer (Examples 12 and 16) and prostate cancer (Examples 19, 20, and 22, Table 19). Thus, the specification demonstrates synergistic combinations for both (-)-gossypol and racemic gossypol, for the secondary agents docetaxel, paclitaxel, and radiation, and for both breast cancer and prostate cancer. These data are more than adequate to support non-obviousness for the entire scope of the present claims.

It is respectfully requested that the rejection of claims 52-55, 60, 61, 78-80, 82-93, and 96 under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for

any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

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